REMARKS

Applicant wishes to thank Supervisor Housel for the courtesy extended to Nancy Vensko, attorney of record, on July 21, 2005. The Interview Summary Form PTOL-413A summarizes the discussion held at the personal interview. The present response to the outstanding Office Action includes the substance of the Examiner Interview.

A. Disposition of Claims

Claims 2-11 and 37-39 are pending in the application. Support for the claims is found in original Claim 1 and throughout the Specification, for example, at page 2, lines 32-35 ("The nucleotide and deduced amino acid sequences among isolates within a quasispecies generally differ by < 2%, whereas those between isolates of different genotypes vary by as much as 35%."), at page 38, lines 12-34 ("The ORF of HC-J6$_{CH}$ was amplified in 3 fragments by RT-PCR (Fig. 1). ... **A quasispecies was found** ..."), and at page 39, lines 11-15 ("The difference between the consensus ORF sequence of HC-J6$_{CH}$ from the experimentally infected chimpanzee and that of HC-J6 of the inoculum (Okamoto et al., 1991) was **4.1%** and **2.2%** at the nucleotide and deduced amino acid levels, respectively (Fig. 2, Table 2).") See also Table 2 at page 40 showing that the percent difference of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ **as measured from nucleotide position 341-9439, which corresponds to the ORF**, is **4.1% at the nucleotide level** and the percent difference of predicted amino acid sequence between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ is **2.2% at the amino acid level**. No new matter has been added.

B. Compliance with 35 USC 102/103

The Patent Office rejected the claims under 35 USC 102(b) as anticipated by Okamoto et al. (EP 532 167 A2) or Okamoto et al. (USP 5,428,145).

Additionally, the Patent Office rejected the claims under 35 USC 103(a) as unpatentable over Okamoto et al. (USP 5,428,145) and Yoo et al. 1995 J. Virol. 69: 32.

Claims 38 and 39 are deemed by the Patent Office free of art. The claims must be patentable over the prior art. The references do not constitute patentability-defeating prior art.

Starting with the general state of the art, according to Yanagi et al., 1999 Virology 262: 250,

at p. 250, ¶ bridging col. 1 & 2, of record, HCV is a virus that has a positive-sense single-strand RNA genome approximately 9.6 kb in length. The single long open reading frame (ORF), which encodes a polyprotein, is flanked by 5' and 3' untranslated regions (UTRs). The 5' UTR contains an internal ribosome entry site (IRES). The 3' UTR consists of 3 regions: a short variable region, a polypyrimidine tract of variable length, and a highly conserved terminal region of approximately 100 nts. The polypyrimidine tract and the conserved region of the 3' UTR are essential for infectivity in vivo.

Turning to the references, Okamoto et al. (EP 532 167 A2) and Okamoto et al. (USP 5,428,145) both describe the cDNA of the isolate HC-J6 but do not describe the highly conserved terminal region of approximately 100 nts essential for infectivity in vivo. Doorn et al. 1995 J. Gen. Virol. 76: 1871 (no longer cited as prior art) classifies HC-J6 as genotype 2a (see Fig. 1 on page 1873). Rice et al. (USP 5,874,565) (no longer cited as prior art) describes the highly conserved terminal region of approximately 100 nts that turns out to be essential for infectivity in vivo. Yoo et al. describes transfection of a differentiated human hepatoma cell line with in vitro-transcribed HCV RNA that lacks the polypyrimidine tract and the highly conserved terminal region of approximately 100 nts essential for infectivity in vivo (see p. 33, col. 2, "results," and FIG. 1), thus infectivity in vivo would be prevented and any perceived infectivity in vitro was probably an artifact. **The claims distinguish over clones that lack the polypyrimidine tract and the highly conserved terminal region of approximately 100 nts of the 3' UTR essential for infectivity in vivo by virtue of the requirement "capable of infectivity in vivo".** The references, whether taken singularly or together, neither teach nor suggest the claimed invention.

The claims as amended are directed to:

> 2. A purified and isolated nucleic acid molecule which encodes human hepatitis C virus of genotype 2a, said molecule capable of expressing said virus when transfected into cells and further capable of infectivity in vivo, wherein said molecule encodes the amino acid sequence of SEQ ID NO: 2 or encodes an amino acid sequence that differs from that of SEQ ID NO: 2 **by < 2.2%** at the amino acid level.

or:

> 3. The nucleic acid molecule of claim 2, wherein said molecule comprises the nucleic acid sequence of SEQ ID NO: 1 or comprises a nucleic acid sequence that differs from that of SEQ ID NO: 1 **from nucleotide 341 to 9439, which corresponds to the ORF, by < 4.1%** at the nucleotide level.

In previously submitted Declaration under 37 CFR 1.132 of Raymond Smith, Ph.D., Dr. Smith compared the percent difference of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ **as measured from nucleotide position 341-9439, which corresponds to the ORF**, and the percent difference of predicted amino acid sequence between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$. Dr. Smith determined that the percent identity of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ **as measured from nucleotide position 341-9439, which corresponds to the ORF**, is **95.9% at the nucleotide level** and the percent identity of predicted amino acid sequence between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ is **97.8% at the amino acid level.** Thus, the evidence shows that the percent difference of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ **as measured from nucleotide position 341-9439, which corresponds to the ORF**, is **4.1% at the nucleotide level** and the percent difference of predicted amino acid sequence between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ is **2.2% at the amino acid level.**

Importantly, the Patent Office is actually in complete agreement with this position. First, the Patent Office compared the percent difference of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ **but forgot to measure from nucleotide position 341-9439, which corresponds to the ORF**. If the Patent Office were to **measure from nucleotide position 341-9439, which corresponds to the ORF,** then the Patent Office would determine that the percent identity of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ is **95.9% at the nucleotide level**. Thus, the evidence would show that the percent difference of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ **as measured from nucleotide position 341-9439, which corresponds to the ORF**, is **4.1% at the nucleotide level**.

As proof, attached is Exhibit A showing the 5-prime end of the Patent Office's comparison of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ and the beginning of the ORF. Exhibit A shows that 2 nucleotides were incorrectly counted as mismatches because they are 5-prime to the beginning of the ORF. Also attached is Exhibit B showing the 3-prime end of the Patent Office's comparison of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ and the conclusion of the ORF. Exhibit B shows that 6 nucleotides were incorrectly counted as mismatches because they are 3-prime to the conclusion of the ORF. Additionally, please be informed that Okomoto USP mistakenly reported nucleotides 7736 and 7737 as GG in SEQ ID NOS: 1 and 2 instead of AA per Okamoto et al. 1991 having Genbank accession number of D00944.1, that GGC does not encode Asn while and AAC encodes Asn, and that Okomoto USP correctly reported amino acid 2466 as Asn in SEQ ID NO: 5 even though Okomoto USP mistakenly reported nucleotides 7736 and 7737 as GG in SEQ ID NOS: 1 and 2. Thus, 2 nucleotides were incorrectly counted as mismatches. In total, 10 nucleotides were incorrectly counted as mismatches. Hence, in order to calculate the number of mismatches in the ORF, one must subtract 10 from the given number of mismatches in the Patent Office's comparison, which is 386, to arrive at the correct number of mismatches, which is 376. The total number of nucleotides encoding the ORF is 9099, per Specification at Table 2 (on page 40). The math shows that 376 mismatches out of 9099 nucleotides calculates to **95.9%** identity. (The Patent Office incorrectly cited 96.0% as shown by "**Best Local Similarity**.") Therefore, the percent difference at the nucleotide level is rightly **4.1%.** In principle (so long as it remembers **to measure from nucleotide position 341-9439, which corresponds to the ORF**), the Patent Office agrees that the percent difference of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ **as measured from nucleotide position 341-9439, which corresponds to the ORF**, is **4.1% at the nucleotide level.**

Second, the Patent Office compared the percent difference of predicted amino acid sequence between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$. The Patent Office correctly determined that the percent identity of predicted amino acid sequence between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ is **97.8% at the amino acid level.** As proof, attached is Exhibit C showing the amino terminus of the Patent Office's comparison of predicted amino acid sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$. The

number of mismatches is given as 30 + 37 = 67. Additionally, to repeat, please be informed that Okomoto USP mistakenly reported nucleotides 7736 and 7737 as GG in SEQ ID NOS: 1 and 2 instead of AA per Okamoto et al. 1991 having Genbank accession number of D00944.1, that GGC does not encode Asn while and AAC encodes Asn, and that Okomoto USP correctly reported amino acid 2466 as Asn in SEQ ID NO: 5 even though Okomoto USP mistakenly reported nucleotides 7736 and 7737 as GG in SEQ ID NOS: 1 and 2. Regardless, for the sake of expediency, we will accept the number of mismatches as 67 (despite it really being 66). The total number of amino acids in the ORF is 3033, per Specification at Table 2 (on page 40). The math shows that 67 mismatches out of 3033 amino acids calculates to **97.8%** identity. The Patent Office correctly cited 97.79%, which rounds out to 97.8%, as shown by "**Best Local Similarity**." Therefore, the percent difference at the amino acid level is rightly **2.2%.** In practice, the Patent Office agrees that the percent difference of predicted amino acid sequence between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ is **2.2% at the amino acid level.**

For these reasons, the references, whether taken singularly or together, neither teach nor suggest the claimed invention, and thus the rejections under 35 USC 102/103 should be withdrawn.

C. Compliance with 35 USC 112/1 written description and 35 USC 132

The issue is whether the claims are in compliance with 35 USC 112/1 written description requirement and 35 USC 132. The rule under MPEP 2163 is that: The written description requirement for a claimed invention may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Referring to examiner training materials available on-line at http://www.uspto.gov/web/menu/written.pdf, which reasons that a claim directed to a product **defined by having at least 95% identity to a SEQ ID NO. and by a function** meets the written description requirement (per Example 14 entitled "Product by Function"), Applicant responds as follows.

First, to reiterate, support for the claims is found in original Claim 1 and throughout the Specification, for example, at page 2, lines 32-35 ("The nucleotide and deduced amino acid sequences among isolates within a quasispecies generally differ by < 2%, whereas those between isolates of different genotypes vary by as much as 35%."), at page 38, lines 12-34 ("The ORF of HC-J6$_{CH}$ was amplified in 3 fragments by RT-PCR (Fig. 1). ... **A quasispecies was found** ..."), and at page 39, lines 11-15 ("The difference between the consensus ORF sequence of HC-J6$_{CH}$ from the experimentally infected chimpanzee and that of HC-J6 of the inoculum (Okamoto et al., 1991) was **4.1%** and **2.2%** at the nucleotide and deduced amino acid levels, respectively (Fig. 2, Table 2).") See also Table 2 at page 40 showing that the percent difference of nucleotide sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ **as measured from nucleotide position 341-9439, which corresponds to the ORF**, is **4.1% at the nucleotide level** and the percent difference of predicted amino acid sequence between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6$_{CH}$ is **2.2% at the amino acid level**. No new matter has been added.

Second, the specification exemplifies a consensus molecular clone of genotype 2a (Example 1) that is infectious in vivo (Example 3). The consensus sequence of strain HC-J6$_{CH}$ could be determined with no ambiguity (Example 1). The difference between the consensus ORF sequence of HC-J6$_{CH}$ from the experimentally infected chimpanzee and that of HC-J6 of the inoculum (Okamoto et al., 1991) was **4.1%** and **2.2%** at the nucleotide and deduced amino acid levels, respectively (Table 2). The specification also contemplates a quasispecies (page 2, lines 32-35) and indicates that a quasispecies was found (page 38, lines 12-34). The specification acknowledges that procedures for making a quasispecies is routine in the art (e.g., Spec at p. 13, line 27 – p. 14, line 3) and provides assays for detecting infectivity in vivo (e.g., Spec at Example 3). Claim 2 is directed to a molecular clone of genotype 2a encoding the amino acid sequence of SEQ ID NO: 2 or encoding an amino acid sequence that differs from that of SEQ ID NO: 2 **by < 2.2%** at the amino acid level. Claim 3 is directed to a molecular clone of genotype 2a comprising the nucleic acid sequence of SEQ ID NO: 1 or comprising a nucleic acid sequence that differs from that of SEQ ID NO: 1 **from nucleotide 341 to 9439, which corresponds to the ORF, by < 4.1%** at the nucleotide level. **To repeat, the claims distinguish over clones that lack the polypyrimidine tract and the highly conserved terminal region of approximately 100 nts of the 3' UTR essential for infectivity in vivo by virtue of the requirement "capable**

of infectivity in vivo". Accordingly, the procedures for making a quasispecies are conventional in the art and assays are described that will identify other molecular clones having the claimed infectivity in vivo. Moreover, procedures for making a molecular clone of genotype 2a encoding the amino acid sequence of SEQ ID NO: 2 or encoding an amino acid sequence that differs from that of SEQ ID NO: 2 **by < 2.2%** at the amino acid level, or comprising the nucleic acid sequence of SEQ ID NO: 1 or comprising a nucleic acid sequence that differs from that of SEQ ID NO: 1 **from nucleotide 341 to 9439, which corresponds to the ORF, by < 4.1%** at the nucleotide level, and possessing the requisite infectivity in vivo, are conventional in the art. A review of the claims indicates that all molecular clones must possess the specified infectivity in vivo and must encode the amino acid sequence of SEQ ID NO: 2 or encode an amino acid sequence that differs from that of SEQ ID NO: 2 **by < 2.2%** at the amino acid level, or must comprise the nucleic acid sequence of SEQ ID NO: 1 or comprise a nucleic acid sequence that differs from that of SEQ ID NO: 1 **from nucleotide 341 to 9439, which corresponds to the ORF, by < 4.1%** at the nucleotide level. A quasispecies must encode the amino acid sequence of SEQ ID NO: 2 or encode an amino acid sequence that differs from that of SEQ ID NO: 2 **by < 2.2%** at the amino acid level, or must comprise the nucleic acid sequence of SEQ ID NO: 1 or comprise a nucleic acid sequence that differs from that of SEQ ID NO: 1 **from nucleotide 341 to 9439, which corresponds to the ORF, by < 4.1%** at the nucleotide level, and possess the requisite infectivity in vivo. The specification indicates that the genus of molecular clones of genotype 2a that must be a quasispecies does not have substantial variation because all of the molecular clones must possess the specified infectivity in vivo and must encode the amino acid sequence of SEQ ID NO: 2 or encode an amino acid sequence that differs from that of SEQ ID NO: 2 **by < 2.2%** at the amino acid level, or must comprise the nucleic acid sequence of SEQ ID NO: 1 or comprise a nucleic acid sequence that differs from that of SEQ ID NO: 1 **from nucleotide 341 to 9439, which corresponds to the ORF, by < 4.1%** at the nucleotide level. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus. The conclusion is that the claims meet the requirement of 35 USC 112/1 written description requirement and 35 USC 132.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 8/25/05

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